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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,856	02/10/2006	Masayuki Tsuchiya	053466-0412	5614

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EXAMINER	
DAHLE, CHUN WU	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,856	TSUCHIYA ET AL.	
	Examiner	Art Unit	
	CHUN DAHLE	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/20/2009 and* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 9-15* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 9, and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission, filed on November 20, 2009, has been entered.

2. Applicant's amendment to the claims, filed on October 20, 2009, has been entered.

Claims 6-8 have been canceled.

Claims 1-5 and 9-15 are pending.

Claims 10-12 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 6, 2008.

Claims 1-5, 9, and 13-15 are currently under consideration as they read on originally elected invention of a sugar chain-altered anti-HM1.24 antibody.

3. This Office Action will be in response to applicant's arguments, filed on October 20, 2009.

The rejections of record can be found in the previous Office Action, mailed on January 6, 2009 and July 28, 2009.

4. The following Non-Patent Literature references cited by application in the REMARKS filed on October 20, 2009 are listed on PTO-892. Copies of these references are not provided herein.

Jenkins, N. et al. (1994), "Glycosylation of recombinant proteins: Problemsand prospects" Enzyme Microb. Technol., 16, 354-364.

Gawlitzek, M. et al. (1995), "Characterization of changes in the glycosylation pattern of recombinant proteins from BHK-21 cells due to different culture conditions" J. Biotechnol., 42, 117-131.

Schweikart, F. et al. (1999), "Rapid structural characterisation of a murine monoclonal IgA o~ chain: heterogeneity in the oligosaccharide structures at a specific site in samples produced in different bioreactor systems" J. Biotechnol., 69, 191-201.

Restelli, V. et al. (2006), "The Effect of Dissolved Oxygen on the Production and the Glycosylation Profile of Recombinant Human Erythropoietin Produced From CHO Cells" Biotechnol. Bioeng., 94(3), 481-494.

Covic, A. et al. (2007), "Biosimilars: recent developments" Int. Urol. Nephrol., 39:261-266.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-5, 9, and 13-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Kanda et al. (US Patent Application 2003/0115614, reference on PTO-892 mailed on January 9, 2008) for reasons of record.

Applicant's arguments, filed on October 20, 2009, have been fully considered but have not been found persuasive.

Applicant has not disputed that Kanda et al. teach anti-HM1.24 antibody but argues that Kanda's method of producing antibody would not have inherently yielded the N-glycoside-linked sugar as claimed. Applicant argues that glycosylation, especially fucosylation, is strongly affected by the growth conditions as demonstrated in Jenkins, N. et al. (Enzyme Microb. Technol., 1994, 16, 354-364), Gawlitzek, M. et al. (J. Biotechnol., 1995, 42, 117-131), Schweikart, F. et al. (J. Biotechnol., 1999, 69, 191-201), Restelli, V. et al. (Biotechnol. Bioeng., 2006, 94(3), 481-494), and Covic, A. et al. (Int. Urol. Nephrol., 2007, 39:261-266). Applicant asserts that identical host cells lines do not result in identical glycosylation patterns. Thus, applicant asserts that Kanda et al. using the same host cells would not necessarily inherently produce the same N-glycan as the instant claims.

Further, applicant asserts that the instant anti-HM1.24 antibody comprsies a sugar chain comprsing a basice structure of Manβ1-4GlcNAcβ1-4GlcNAc-PA wherein said sugar chain does nto constan α1,6 core fucose but contains a bisecting N-GlcNAc wihd is bound with β1,4-linkage on the Man of the basic structure. Applicant further asserts that the instant specification discloses that the bisecting GlcNAc chain in 11.3% of all sugar chains and of the bisecting GlcNAc sugar chians, 29% were fucose-free. As such applicant asserts that Kanda et al. do not meet the claimed sugar structure because Kanda et al. teach only a very small amount of bisecting GlcNAc sugar chain and fucosylated.

Therefore, applicant argues that Kanda et al. do not meet the claimed limitation and the rejection should be withdrawn.

This is not found persuasive for following reasons:

The Examiner acknowledges that cell culture conditions would probably contribute to the percentage of the content of N-glycan. However, the genetic contents of the host cells (e.g. genes

encoding glycosylation enzymes) would determine the structure of the N-glycan on the glycoproteins being produced. Here, contrary to applicant's assertion that the host cells, e.g. engineered YB2/0, would not inherently produce the N-glycan structure being claimed, it is noted that the instant sugar chain altered anti-HM1.24 antibody is produced in YB2/0 because YB2/0 has low fucose transferring activity (e.g. see page 10 of the instant specification or see copy below)

> *"In accordance with the present invention, any cells that have no or low fucose-transferring ability can be used and, as a specific example, there can be mentioned the rat myeloma YB2/3HL.P2.GII.16Ag.20 cells (abbreviated as the YB2/0 cell) (stored as ATCC CRL 1662)"*

Kanda et al. teaches methods of producing antibody in host cells including YB2/0 genetically engineered to have fucose transferase deleted (e.g. see claims 23-39). Thus, it is reasonable to conclude that the prior art host cells would produce an antibody without fucose. Applicant has not submitted objective evidence to show that engineered host cells taught by Kanda et al. (e.g. YB2/0 with fucose transferase knock-out) would not produce an antibody having the N-glycan as claimed.

Although the reference is silent about the antibody the antibody having a sugar chain including the basic structure as claimed and does not contain α1,6 core fucose but contains a bisecting GlcNAc bound with a β1,4-linkage on the mannose, it does not mean that the reference antibody does not have these N-linked sugar structure. Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody produced in engineered host cells including YB2/o with fucose transferase knockout does not have the sugar chain structure as recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

With respect to applicant's arguments relying upon the percentage of bisecting GlcNAc disclosed in the instant specification, it is noted that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). See MPEP 2145. In this case, the instant claims 1-5 and 13-15 do not recite percentage of bisecting GlcNAc while claim 9 is drawn to fucose-free sugar chain of 30% or more, it does not recite percentage of bisecting GlcNAc. Since the prior art antibody is produced in host cells without fucose transferase, it is reasonable to conclude the antibody would not have fucose, thus would meet the claimed fucose free sugar chain of 30% or more.

Therefore, applicant's arguments have not been found persuasive.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-5, 9, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ono et al. (US 6,699,974) in view of Umana et al. (US 6,602,684) as evidenced by the instant disclosure of host cell expressing GnT III (e.g. in CHO cells) for making the claimed HM1.24 antibody in page 11 and pages 22-23 of the instant specification

Ono et al. teach humanized anti-HM1.24 antibodies exhibiting effector functions including antibody dependent cell mediated cytotoxicity (ADCC) is therapeutically effective to treat B cell malignancy (e.g. see claims 1-9 and columns 37-70).

The reference teachings differ from the claimed invention by not describing a sugar chain altered anti-HM1.24 antibody.

Umana et. al. teach that therapeutical antibodies relying upon effector functions (e.g. ADCC) can be produced in glycosylation engineered host cells wherein the host cells express β1,4 N-acetylglucosaminyltransferase (GnT III) for increased ADCC function (e.g. see claims 1-10). Further, Umana et al. characterized the N-glycan of said antibodies to be Manβ1-4GlcNAcβ1-4GlcNAc core structure and without core fucose but have bisecting GlcNAc (e.g. see Figures 9-11). Furthermore, Umana et al. teach that antibodies produced in the engineered host cells expressing GnT III have higher accumulation of non-fucosylated bisecting sugar chain because N-linked oligosaccharides which are first modified by GnT III can no longer be biosynthetic substrates for core α1,6-fucosylaltransferase (e.g. see column 26 and Figures 9-11). Umana et al. teach that said antibody having altered glycoform exhibits improved therapeutic properties via enhanced ADCC function (e.g. see column 2).

It would thus be obvious to one of skill in the art to produce humanized anti-HM1.24 antibody taught by Ono et al. using GnT III engineered host cells taught by Umana et al. because anti-HM1.24 antibody exhibiting ADCC function is therapeutically effective in treating B cell malignancy and antibodies produced in GnTIII engineered host cells would have altered glycan structure, which in term, exhibits enhanced ADCC function. One of ordinary artisan would have been motivated to do so because Ono et al. teach that humanized anti-HM1.24 antibody with ADCC function is therapeutically effective in treating B cell lymphoma and Umana et al. teach methods of increasing ADCC function of therapeutic antibody by alter it N-glycan structure.

As evidenced by the instant disclosure, the claimed antibody can be produced in host cells engineered to express GnT III enzyme (see pages 11 and 22-23 of the instant specification). Thus, the humanized anti-HM1.24 antibody produced in Umana's host cells engineered in the

same manner as the instant application (expressing GnT III) would be expected to have the same N-glycan structure as the instant claims.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Dahle whose telephone number is 571-272-8142. The examiner can normally be reached on 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Ram Shukla can be reached 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Chun Dahle/
Primary Examiner, Art Unit 1644